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ARTICLE

Economic burden of adverse drug reactions and potential for pharmacogenomic testing in Singaporean adults

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Abstract

Adverse drug reactions (ADRs) contribute to hospitalization but data on its economic burden is scant. Pre-emptive pharmacogenetic (PGx) testing can potentially reduce ADRs and its associated costs. The objectives of this study were to quantify the economic burden of ADRs and to estimate the breakeven cost of pre-emptive PGx testing in Singapore. We collected itemized costs for 1000 random non-elective hospitalizations of adults admitted to a tertiary-care general hospital in Singapore. The presence of ADRs at admission and their clinical characteristics were reported previously. The economic burden of ADRs was assessed from two perspectives: (1) Total cost and (2) incremental costs. The breakeven cost of PGx testing was estimated by dividing avoidable hospitalization costs for ADRs due to selected drugs by the number of patients taking those drugs. The total cost of 81 admissions caused by ADRs was US$570,404. Costs were significantly higher for bleeding/elevated international normalized ratio (US$9906 vs. US$2251, $p = 6.58 \times 10^{-3}$) compared to other ADRs, and for drugs acting on the blood coagulation system (US$9884 vs. US$2229, $p = 4.41 \times 10^{-3}$) compared to other drug classes. There were higher incremental laboratory costs due to ADRs causing or being present at admission. The estimated breakeven cost of a pre-emptive PGx test for patients taking warfarin, clopidogrel, chemotherapeutic and neuropsychiatric drugs was US$114 per patient. These results suggest that future studies designed to directly measure the clinical and cost impact of a pre-emptive genotyping program will help inform clinical practice and health policy decisions.

Introduction

Adverse drug reactions (ADRs) are known to contribute to worse patient outcomes and increased hospital admissions [1]. We have previously reported a prospective study in 1000 random non-elective hospitalizations of adults admitted to a tertiary acute care hospital in Singapore, a multiethnic island city state in Southeast Asia, and found

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that 12.4% of patients have at least one ADR at admission and 8.1% of admissions were caused by an ADR [2]. Data on ADR-associated costs in Singapore are scant. In a recent study, ADRs were identified using International Classification of Diseases (ICD) codes in patients ≥ 65 years old, and the median hospitalization cost per patient with ADRs was estimated to be $1015 (2013 SGD, approximately US $811) [3]. On the higher end, the median cost of hospitalization for chemotherapy-induced febrile neutropenia in cancer patients was $3964 (2012 SGD, approximately US $3171) [4]. The cost of other ADRs in the general population is unknown.

Studies in the Netherlands, Germany, and Canada have documented substantial annual national ADR-related costs in the order of 1050 million Deutsche Mark (DM) (~US $732 million in 1995), €355 million (~US$441 million in 2004), and Canadian $35.7 million (~US$33.3 million in 2007), respectively [5–7]. In the Netherlands, the direct cost attributable to ADRs constitutes 2.4% of the national healthcare budget [6]. In India, the absolute ADR-related costs were much lower than in developed countries, likely a reflection of the lower cost of living there. However, the average cost per patient hospitalized with an ADR (US$ 115) was higher than the national per capita annual health expenditure (US$ 109) [8]. Hence, it is vital to design strategies to reduce cost burden associated with ADRs.

Our team previously conducted a prospective study on 1000 randomly selected adults admitted non-electively to a large tertiary hospital to evaluate the presence of ADRs at the point of admission. The prevalence of ADRs at admission was 12.4% and that of ADRs causing the admission was 8.1%. Furthermore, 30 of the 81 ADRs causing admission had a pharmacogenetic (PGx) association, suggesting a potential for prevention through PGx testing [2].

Most initial efforts to implement PGx have been on a reactive single-variant basis at the point of drug prescription, which may not provide the needed information in a timely fashion and incurs a cost for each test of a different variant. Pre-emptive PGx programs, where multiple genetic variants are genotyped and stored in electronic medical records prior to drug prescription, is an alternative strategy that is more practical and likely more cost-effective than reactive, single-variant genotyping [9]. Experience shared by the early adopters of pre-emptive PGx testing revealed some variation in its implementation, such as the panel used, patient population tested and so on [9]. As this pre-emptive strategy is still in its infancy, it is not currently covered by insurance [10]. More studies to evaluate the clinical outcomes, cost-effectiveness and to define target populations will be needed to support regulatory and payer decisions on pre-emptive PGx testing [11].

In Singapore, genotyping for *HLA-B*15:02* allele is performed prior to initiation of carbamazepine therapy in patients of Asian ancestry as standard of care for the avoidance of Steven's Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) [12]. A cost-effectiveness analysis supported the decision by the Ministry of Health to subsidize the cost of the genotyping test. As a result, the number of cases of carbamazepine-associated SJS/TEN has dropped sharply from an average of 18 cases per year to only one case over 4 years after the implementation of *HLA-B*15:02* testing [12]. This precedent may herald more of such PGx tests that demonstrate both clinical efficacy and cost-effectiveness. However, multiple single drug-gene tests incur repeated fixed costs such as blood collection, DNA extraction, PCR amplification that could be avoided through multiple allele genotyping panels and next generation sequencing. The genetic information would also be available at the time of prescribing, rather than having to wait for return of results from single-gene tests. As such, the future is trending towards pre-emptive PGx panel testing.

Most cost-effectiveness analyses (CEA) of PGx testing conducted thus far have been for single drug-gene pairs. One study found a one-time PGx test for a panel of markers cost-effective for preventing lifetime ADRs at a price of US$1102 per test [13]. This study, however, did not include costs of alternative drugs for patients found to be unsuitable for the standard treatments based on genotype and the variability of hospitalization costs for different ADRs. To the best of our knowledge, detailed modeling of all possible outcomes in a PGx testing scenario for a CEA beyond one single drug-gene pair has not been done, likely due to its extreme complexity. Encouragingly, 75% of pharmacoeconomic evaluations of PGx testing favored it [14] and a discrete-choice experiment in Singapore showed that majority of patients were willing to pay several hundred dollars out-of-pocket for PGx tests to reduce ADR risk [15]. Given the expanding knowledgebase of associations between genetic variation and safe and efficacious use of drugs [16], there is a growing interest in quantifying the economic costs and benefits of pre-emptive PGx testing [17].

The objectives of this study were twofold. First, we aimed to quantify the economic burden of ADRs in the general adult population in Singapore. The total as well as incremental costs associated with ADRs were investigated. Second, we aimed to gauge the potential of a pre-emptive PGx program for prevention of ADRs in Singapore, by estimating the breakeven cost of pre-emptive PGx testing.

Materials and methods

Patient population

Details of patient recruitment, data collection and ADR ascertainment were described previously [2]. Briefly, the

patient cohort consisted of 1000 randomly selected adults admitted non-electively to the Singapore General Hospital (SGH), the largest acute care hospital in Singapore. Demographic and clinical information were collected, and each patient was screened for ADRs at admission based on the drugs taken before admission and the presenting complaints. Suspected ADRs were formally assessed by two investigators using the Liverpool Causality Assessment Tool (LCAT), an algorithm that classifies ADRs into one of four categories (definite, probable, possible and unlikely) based on a series of up to ten questions about the characteristics of the ADR [18]. We evaluated 351 potential ADRs in 254 out of 1000 admissions using the LCAT, but included only 'definite' and 'probable' ADRs (higher certainty that reaction was linked to suspected drug) in the prevalence calculations and subsequent analyses for a more conservative estimation [2]. Itemized bills were retrieved from the finance billing database of SGH for all 1000 patients. The bills reflect the amount before any patient subsidy and represents the cost to the health system. This study was approved by the ethics committee of SGH with waiver of informed consent.

Economic analysis

All analyses were undertaken from a health system perspective, thus prices before any government subsidy were used in all calculations. Only direct medical costs related to hospital admissions were considered, as this is known to be the largest cost item. All costs were converted to US$ using 2016 exchange rates (US$1 = SGD 1.382) [19].

Total cost of ADRs

The total cost of ADRs was the sum of costs of hospitalizations caused by ADRs. We then further stratified based on demographic, clinical and ADR characteristics (e.g., causality, severity, PGx association, etc) to understand the nature of the ADRs that posed the greatest economic burden. Given the variety of ADRs, we performed a subgroup analysis on the five most common ADR types and suspected drug classes. The Wilcoxon signed rank test or Spearman rank correlation were used as appropriate.

Incremental costs of ADRs

To estimate the incremental economic burden due to the presence of ADRs at the point of admission, we compared the cost differences for two groups of patients (admissions caused by ADRs, and admissions presenting with but not caused by ADRs) with controls (admissions without ADRs). For both groups of cases, we performed propensity score matching to select controls. For the propensity score model, all demographic and clinical variables were included with exact matching imposed for ward type, place of admission (emergency department or specialist outpatient clinics), having a cardiovascular condition, having cancer and Charlson's comorbidity index (CCI). These variables were chosen for exact matching as they had the greatest effect on cost. CCI was calculated from clinical information collected at admission [20]. Propensity score matching was performed using the nearest-neighbour method with a caliper of 0.25 standard deviations and a ratio of one. Alternative propensity score models were explored, and this final model was chosen because of better matching of important characteristics and overall propensity scores. All models explored are shown in Tables S1 and S2. The cost difference between cases and controls was analyzed using the Wilcoxon sign rank test and expressed as the median of differences between each matched pair. We also analyzed differences by different cost categories (ward, drugs, labs, other investigations, treatments and procedures, service and facility fees, and consumables). Propensity score matching was performed using the MatchIt package version 3.0.1 in R version 3.3.3 [21].

Estimation of breakeven cost of PGx testing

We performed a simple estimation of the maximum cost of a hypothetical PGx panel testing at which the savings from avoiding ADR associated hospitalizations will be offset. Out of the 81 admissions caused by 'definite' or 'probable' ADRs in our previous study of 1000 adults admitted non-electively, 30 involved a drug-gene pair with a PGx association [2] with levels of evidence between 1A and 3 according to PharmGKB. We limited this hypothetical PGx panel to drug-gene pairs for which there are data on efficacy from prospective trials of PGx testing vs. no testing, i.e. warfarin, clopidogrel, chemotherapeutic and neuropsychiatric (anti-depressants, anti-psychotics and anxiolytics) drugs. The potential savings from avoided ADRs was estimated by the sum of the product of efficacy of PGx testing and total cost of ADRs due to each drug(s) within the previous ADR study [2]. This amount was then extrapolated to the entire Singapore population over a year, assuming 63% of all adult admissions are non-elective (estimated from recruitment statistics from a previous survey performed in Singapore [2]). We then estimated the number of patients at risk of ADRs (number of patients taking at least one of the drugs mentioned) in the entire Singapore population (residents and non-residents) in 2016 using disease incidence or prevalence data for the common indications of those drugs. The indications were considered individually, so the estimated total number of patients at risk of ADRs (and therefore number of patients to be tested)

is the sum of patients with each indication. The breakeven cost was then the potential savings from ADR avoidance divided by the number of patients at risk of ADRs due to the four drugs/drug classes. All analyses were carried out in R version 3.3.3 [22].

Results

Out of 1000 admissions, 124 had an ADR present at the point of admission, of which 81 were caused by the ADR [2]. Cost data were retrievable for 995 out of 1000 admissions, including all 124 admissions with ADRs at admission. The median hospitalization cost was US$2800 (range, US$416–U$82489).

Total cost of ADRs

The total cost of the 81 admissions caused by ADRs was US$570,404, constituting 10.1% of the total hospitalization cost of the 995 patients. The median cost for these admissions was US$2951 (range, US$591–US$81,476). Table 1 showed the breakdown by different cost categories. Table 2 showed the differences in cost by various demographic, clinical and ADR characteristics. Among these admissions, cost was significantly higher for surgical disciplines ($p = 0.031$) and higher CCI ($p = 2.4 \times 10^{-4}$). Among ADR characteristics, there was a trend towards higher costs with higher number of ADRs ($p = 0.046$), significantly higher costs for drug-ADR pairs with PGx association ($p = 0.027$) and with higher severity of the ADRs ($p = 8.62 \times 10^{-4}$). Of the top five ADR types and drug classes, costs were significantly higher with bleeding/elevated international normalized ratio (INR) (US$9906 vs. US$2251, $p = 6.58 \times 10^{-3}$) and drugs acting on the blood coagulation system (US$9884 vs. US

Table 1 Total cost of ADRs by categories of expenses

Category	Total (US$)
Drugs	$49,762
Laboratory investigations	$108,315
Other investigations	$81,426
Treatments and procedures	$66,993
Service and facility fees[a]	$51,643
Consumables and miscellaneous	$38,934
Ward[b]	$173,329
Total	$570,404

This table shows the total cost for the 81 patients with admissions caused by ADRs, rounded to the nearest dollar.

[a]Includes professional fees

[b]Bed charges only. Does not include daily treatment fee, procedures, medications, laboratory tests, imaging, etc.

Table 2 Total cost of admissions caused by ADRs by demographic, clinical and ADR characteristics

Variable		*N*	US$, median	*p*
Demographic and clinical				
Age		Spearman's rho = −0.225		**0.043**
Gender	Male	44	$3848	0.166
	Female	37	$2229	
Ethnicity	Chinese	57	$2748	0.563
	Malays	10	$5897	
	Indians	12	$2867	
	Others	2	$4894	
Have drug allergies	Yes	26	$2766	0.667
	No	55	$3024	
Ward type	Medical	72	$2766	**0.031**
	Surgical	9	$9903	
Admitted from	ED	60	$2987	0.751
	SOC	21	$2823	
Have a cardiovascular condition[a]	Yes	67	$3059	0.473
	No	14	$2035	
Have cancer	Yes	16	$4041	0.371
	No	65	$2823	
Charlson's comorbidity index		Spearman's rho = 0.415		**1.16×10^{-4}**
No. of drugs taken before admission		Spearman's rho = 0.263		**0.018**
ADR characteristics				
No. of ADRs	1	75	$295	**0.046**
	2	4	$8533	
	3	2	$812	
Drug-ADR pair has PGx association[b]	Yes	30	$4819	**0.027**
	No	51	$2229	
Causality[c]	Definite	24	$4410	0.566
	Probable	57	$2783	
Avoidability[c]	Definitely	3	$7766	0.614
	Possibly	76	$2987	
	Not avoidable	2	$2643	
Severity[c]	1-2	4	$1690	**8.62×10^{-4}**
	3–4	68	$2625	
	5–6	9	$16,724	
Type[c]	A	79	$2951	0.420
	B	2	$7789	

p values were from Wilcoxon signed rank test or Spearman's rank correlation, as appropriate, to test for the association between various variables and total cost among the 81 admission caused by ADRs. The Spearman's rank correlation measures the strength and direction of correlation between two ranked variables and a higher absolute value represents higher correlation. *p* values < 0.05 were considered statistically significant (bolded).

ADR adverse drug reaction, *ED* emergency department, *PGx* pharmacogenetic, *SOC* specialist outpatient clinics

[a]At least one of the following conditions: hypertension, hyperlipidaemia, congestive heart failure, history of myocardial infarction, ischemic heart disease, rheumatic heart disease, atrial fibrillation, coronary artery disease and any arrhythmias.

[b]This refers to a PGx association for the ADR caused.

[c]Causality, avoidability, severity and type were assessed using the Liverpool Causality Assessment Tool [18], the method of Hallas et al. [39], the adapted Hartwig scale [40] and the classification of Rawlins and Thomson [41], respectively. Severity increases with number. Type A ADRs are dose dependent and predictable while type B are not.

Table 3 Total cost of admissions caused by top five ADR types and drug classes

	N	Median (range), US$		*p*
		Yes	No	
ADR type				
Gastrointestinal	18	$1997 ($710–$81,476)	$3024 ($591–$40,311)	0.385
Bleeding/elevated INR	15	$9906 ($1413–$19,327)	$2251 ($591–$81,476)	$\mathbf{6.58 \times 10^{-3}}$
Electrolyte abnormalities	8	$1656 ($783–$6028)	$3024 ($591–$81,476)	0.157
Infection/sepsis	6	$4749 ($1632–$40,311)	$2823 ($591–$81,476)	0.422
Hypotension	6	$2142 ($783–$4381)	$3059 ($591–$81,476)	0.245
Drug class[a]				
Cardiovascular	23	$2229 ($783–$18,907)	$3352 ($591–$81,476)	0.376
Blood	17	$9884 ($1413–$19,327)	$2229 ($591–$81,476)	$\mathbf{4.41 \times 10^{-3}}$
Chemotherapeutic	15	$4438 ($591–$40,311)	$2887 ($710–$81,476)	0.447
Central nervous system	12	$3525 ($842–$30,195)	$2951 ($591–$81,476)	0.755
Musculoskeletal	6	$4804 ($842–$18,907)	$2951 ($591–$81,476)	0.921

p values were from Wilcoxon signed rank test. *p* values < 0.05 were considered statistically significant (bolded).

ADR adverse drug reaction, *INR* international normalized ratio

[a]Suspected drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [42].

$2229, $p = 4.41 \times 10^{-3}$), respectively (Table 3). As warfarin and clopidogrel (the main drugs within the class) are well known to cause bleeding and elevation of INR (warfarin only) and have PGx associations for these clinically important ADRs, the associations for drug classes and PGx associations were likely driven by these ADRs (Figure S1).

Incremental cost of ADRs

For admissions caused by ADRs, 76 of 81 patients were matched using the propensity score model. Baseline characteristics before and after matching are shown in Table S1. The total cost of admissions caused by ADRs was not significantly different from admissions without ADRs ($p = 0.243$), but laboratory costs (such as renal function tests, full blood count, serum electrolytes, and prothrombin time) were significantly higher (median of differences = US$187, $p = 0.005$) (Table 4).

To determine if the presence of an ADR at admission for other causes contributed to increased cost, we also compared the costs for admissions with but not caused by ADRs with those for admissions without ADRs. For these admissions, 37 of the 43 patients were matched using the propensity score model. Characteristics of patients before and after matching are shown in Table S2. Again, the total cost of cases was not significantly different from the controls ($p = 0.561$) but laboratory costs were higher in admissions with but not caused by ADRs (median of differences = US$283, $p = 0.014$) (Table 4).

Breakeven cost of pre-emptive PGx testing

The total cost of the 30 admissions caused by ADRs with a PGx association with the suspected drug was US$214,902. Considering only ADRs due to warfarin, clopidogrel, chemotherapeutic and neuropsychiatric drugs, the total cost of admissions were US$86,650, US$38,621, US$63,276 and US$6368, respectively. Using median PGx efficacies of 31.5% [23–26], 38.4% [27, 28], 80.8% [29], and 47.2% [30], respectively, the total cost potentially avoidable by PGx testing was US$96,258. The estimated number of patients taking at least one drug from the above mentioned list was 247,988 (Table S3). In a hypothetical situation, if all these patients had undergone pre-emptive PGx testing, the breakeven cost of the test would be US$114 per person tested (Table 5).

Discussion

We have quantified the direct economic burden of hospitalizations caused by ADRs in the general adult population. At a rate of US$570,400 per 1000 patients, the direct annual ADR burden in Singapore is estimated to be US$168 million, almost 5% of the annual operating healthcare expenditure [31]. The median cost of US$2951 was also much higher than the SGD1015 (~US$734) reported previously in elderly patients from the same institution, likely because of different ADR detection methods (ICD codes vs. manual review) [3]. In this study, bleeding and/or elevated INR due

Table 4 Incremental costs of ADRs

Cost type	Admissions caused by ADRs		Admissions with but not caused by ADRs	
	Median of differences (95% CI[a]), US$	*p*	Median of differences (95% CI[a]), US$	*p*
Total	$345 (−$496–$2500)	0.243	−$9 (−$1503–$4264)	0.561
Drugs	$48 (−$17–$147)	0.100	−$8 (−$103–$119)	0.941
Laboratory investigations	$187 ($90–$652)	**0.005**	$283 ($99–$1020)	**0.014**
Other investigations	$20 (−$144–$377)	0.412	$212 (−$56–$648)	0.118
Treatments and procedures	$26 (−$98–$350)	0.329	$62 (−$148–$530)	0.265
Ward	$77 (−$47–$839)	0.104	$57 (−$386–$1291)	0.455
Service and facility fees	$0 (−$137–$204)	0.903	$0 (−$305–$898)	0.874
Consumables and misc	−$5 (−$72–$96)	0.912	$7 (−$119–$533)	0.747

The table shows the median of the differences in cost between each pair of cases and controls. *p* values were from Wilcoxon signed rank test and values < 0.05 are bolded. The number of case/control pairs for admissions caused by ADRs and admissions with but not caused by ADRs were 76 and 37, respectively. For both case definitions, the control group was selected from admission with no ADRs at admission

[a]CIs are approximately but at least 95%, due to the discrete nature of the data used in estimation of nonparametric CIs

to anticoagulants or anti-platelets were identified to be the most expensive ADRs. Therefore, efforts to reduce ADRs with these agents are likely to provide the most impact in reducing costs. It should be highlighted that evidence of clinical efficacy of PGx testing is also among the most abundant for this group of ADRs. Failing to act is likely to result in a missed opportunity.

Admissions caused by ADRs as well as admissions with but not caused by ADRs did not incur significantly higher total costs than admissions without ADRs. However, laboratory costs were higher in both groups, likely because of additional laboratory tests required to monitor the ADR until its resolution, such as in the case of over-anticoagulation, electrolyte abnormalities, renal impairment, bone marrow suppression and infection, which made up about half of the ADRs that caused admission.

Over one-third of the ADRs captured in our study had a PGx association, and warfarin, clopidogrel, chemotherapeutic or neuropsychiatric drugs were responsible for 76% of these ADRs. We propose that PGx testing is one avenue towards safer use of these drugs. It has been argued that pre-emptive PGx testing would be more convenient and cost-effective than individual PGx tests administered on a reactive basis [32]. The prevalence of actionable genotypes is >90% across multiple ethnicities [33]. Among Singaporeans, the prevalence of at risk genotypes for warfarin alone is also about 90% [34] but PGx testing for warfarin is not routinely performed. Thus, we have also attempted to estimate the breakeven point at which the cost of pre-emptive PGx testing would equal potential savings for patients receiving drugs with well-established PGx associations. To the best of our knowledge, this is the first study exploring the economics of PGx testing in this way. Hypothetically, if patients requiring warfarin, clopidogrel, chemotherapeutic or neuropsychiatric drugs were pre-emptively tested, the price of the test only needed to be <US$114 to be cost saving at a health systems level. The current price of pre-emptive genotyping panels ranges from US$300 to $2000 [35]. The optimal strategy for pre-emptive PGx testing is still unclear. In our calculations we assume that all patients needing the four drugs/drug classes could be given PGx testing before the drug is administered, perhaps at the point of diagnosis of the condition. Practically, another approach may be testing patients likely to receive the drugs, based on their risk factors, but the assessment of the most cost-beneficial strategy is beyond the scope of this study.

This estimate is likely to be conservative for several reasons. Firstly, costs due to other drugs with PGx associations, costs attributable to ADRs that did not cause hospital admissions, indirect costs and benefits beyond the current admission were not included in the calculation.

Secondly, costs due to adverse outcomes avoided from better response to alternative drugs or optimal doses of drugs were also not included, such as adverse cardiovascular outcomes due to inadequate clopidogrel response, which is associated with a patient's *CYP2C19* genotype [36]. Among the 111 patients taking clopidogrel prior to admission in our cohort, 10 were admitted for myocardial infarction, stroke or thrombosis. While the *CYP2C19* genotypes of these patients are unknown, it is possible that some of these events and their associated costs could have been prevented by PGx testing. Thirdly, the number of patients to test could be over-estimated as some patients

Table 5 Calculation of breakeven cost of pre-emptive PGx testing

	Value, US$	Remarks	Reference
Potential savings by PGx testing[a]			
Within current study			
Warfarin ADRs	$27,295	Efficacy of PGx (31.5%) x total cost for these ADRs (US$86,650)	[23–26]
Clopidogrel ADRs	$14,831	Efficacy of PGx (38.4%) x total cost for these ADRs (US$38,621)	[27, 28]
Chemotherapeutic drug ADRs[b]	$51,127	Efficacy of PGx (80.8%[c]) x total cost for these ADRs (US$63,276)	[29]
Neuropsychiatric drug ADRs	$3006	Efficacy of PGx (47.2%) x total cost for these ADRs (US$6368)	[30]
Total	$96,258		
Estimated total annual cost nationwide	**$28,376,709**	Using no. of adult admissions in 2016 (467,936) and proportion of non-elective admission = 63%	[2, 43]
Number of patients at risk of ADRs due to the 4 drugs/drug classes in 2016			
Estimated number of patients with conditions[d]			
Venous thromboembolism	4099	Indication for warfarin	[44]
Atrial fibrillation	22692		[45]
Heart valve replacement due to aortic stenosis	81		[46]
Myocardial infarction	15331	Indication for clopidogrel	[47]
Ischemic stroke	8583		[48]
Cancer	21176	Indication for chemotherapeutic drugs	[49]
Use of anti-depressants and benzodiazepines	95149	Indication for neuropsychiatric drugs	[37]
Bipolar disorder	28545		[50]
Obsessive compulsive disorder	52332		[51]
Total	**247988**		
Breakeven cost of pre-emptive PGx test	**$114**	Estimated total annual cost nationwide / number of patients at risk of ADRs due to the 4 drugs/drug classes in 2016	

[a]The efficacy of PGx for each drug(s) was the median of % improvement in ADR outcomes for prospective trials of PGx testing vs. no testing. For warfarin, only ADRs and INR > 4 were considered, and for clopidogrel only bleeding ADRs were considered. All-cause mortality was excluded as it is not a specific ADR

[b]Chemotherapeutic drugs with PGx association were included bevacizumab, capecitabine, cisplatin, cyclophosphamide, cytarabine, doxorubicin, methotrexate, oxaliplatin, paclitaxel, vinblastine and vincristine

[c]For fluoropyrimidines

[d]Number of patients with each condition was estimated using age-specific or total (adult) incidences or prevalences and the population structure of the resident adult population of Singapore in 2016 and then extrapolated to the total population. See Table S3 for more details

ADR adverse drug reaction, *PGx* pharmacogenetic

may have overlapping conditions. Also, not all patients with the indications for the selected drugs may be actually receiving it, especially for neuropsychiatric disorders. For example, only 27% of patients with a major depressive disorder consulted a doctor [37]. Finally, death (which occurred in one patient with admission caused by ADR) or reduced quality of life incurs no additional cost in our analysis but are clearly important considerations to patients.

With decreasing genotyping costs, a unit cost of a pre-emptive PGx test on the order of US$114 is quite achievable. A comprehensive PGx panel (which need not be limited to one single technology) that includes all actionable PGx markers can also prevent cases of rare but serious and expensive ADRs such as SJS/TEN, which can cost from US $1740 to US$25,540 per episode [38]. Patients requiring carbamazepine can potentially derive more benefit for no

additional cost over the single *HLA-B*15:02* test, which currently costs SGD200 (~US$145) [12]. The amount that patients are willing to pay may also be much more than US $114. A recent discrete choice experiment among Singaporeans at high risk of developing gout found that two-thirds are risk averse and are willing to pay SGD438 (~US $317) for a modest risk reduction of life-threatening ADRs from one in 600 to one in 1000, and even more for further risk reduction [15].

There are several limitations to our study. Firstly, the number of patients with ADRs at admission is relatively small. This might have affected the precision of our cost calculations. Secondly, the data was from a single institution and the types of patients seen at SGH could be different from that in other hospitals in Singapore. Therefore, the extrapolated costs may be under- or over-estimated. However, that ADR survey was the most comprehensive to date in terms of patient characteristics. Thirdly, causality assessment of ADRs is subjective. However, we have reduced this by having two independent assessors and a third one to resolve any discrepancies. Fourthly, we have only considered cost savings with four drugs or drug classes. Potential savings were likely to be underestimated as other drug-gene pairs with substantial scientific evidence were not included. Fifthly, additional costs arising from use of alternative drugs due to PGx testing results were not taken into account in the calculation. However, the majority of drugs involved in the ADRs we considered require dose reduction instead of more expensive alternative drugs so cost estimates may not be affected significantly. It is possible that treatment response may be suboptimal if doses are reduced and further costs incurred as a result. However, PGx testing is aimed at optimizing response (INR) for warfarin, and PGx trials for chemotherapeutic and neuropsychiatric drugs have demonstrated similar response despite dose reduction [29, 30]. Sixthly, we assumed that the proportion of admissions avoided was the percentage improvement in outcomes from PGx trials but the relationship between the two may not be linear. For example, a 50% reduction in ADRs due to PGx testing may not translate to 50% reduction in ADR-related hospitalization, depending on the type of ADRs. Seventhly, the efficacy of PGx testing for chemotherapeutic drugs was inferred from data for fluoropyrimidines only. Lastly, the estimation of the number of patients receiving the four drugs/drug classes (denominator) in our hypothetical PGx testing involved calculations using the resident population structure and extrapolation to the total population because the potential cost savings (numerator) were extrapolated using the total number of non-elective hospital admissions in Singapore, which was derived from both residents and non-residents. The denominator could be inaccurate due to the lack of information about the population structure of non-residents. However, we believe the non-resident population to be younger as they are mostly students or people on work permits, so we would have likely over-estimated the number needed to test, which would give a more conservative estimate of the breakeven cost.

In conclusion, the costs of 81 cases of ADR-induced hospitalizations in a study of 1000 random, non-elective adult admissions was US$570,400, and bleeding/elevated INR ADRs were significantly more expensive than other ADRs. Admissions caused by or with ADRs incurred higher laboratory costs compared to admissions without ADRs. Finally, the estimated breakeven cost of a pre-emptive PGx test for patients needing warfarin, clopidogrel, chemotherapeutic, or neuropsychiatric drugs was US$114. These results suggest that future studies designed to directly measure the clinical and cost impact of a pre-emptive genotyping program will help inform clinical practice and health policy decisions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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